

REMARKS

Applicants would like to thank the Examiner for the personal interview granted on May 18, 2005 to Applicants' agent Donna Ward and the telephonic interview granted on April 7, 2005 to Applicants' attorney Li-Hsien Rin-Laures and Applicants' agent Donna Ward. In summary, the interview discussion focused on claim language relating to hybridization within nucleotide ranges of SEQ ID NO: 3 and to the term "non-catalytic." It was determined that amendment of the claims to eliminate nucleotide ranges, to recite a functional limitation of 30% inhibition, and to recite "non-cleaving" in place of "non-catalytic" would be looked at favorably.

I. Support for the Amendments

Support for the amendment to claims 1, 11 and 20 can be found throughout the specification. For example, support for recitation of the functional limitation "at least 30% inhibition of apoB expression when applied when applied in vitro at a concentration of 150nM to HepG2 cells" is found in Example 15 at page 88, lines 27-29 which describes that "compounds [in Table 1] were analyzed for their effect on human apolipoprotein B mRNA levels in HepG2 cells by quantitative real-time PCR" and page 90, line 4, which discloses that "at least 30% inhibition of human apolipoprotein B expression in this assay [is] preferred." Additionally, Example 16, at page 91, line 24-25, teaches that selected compounds were further tested at 50, 150 and 250 nM.

Support for amendment to recite "non-cleaving" is found, for example, at page 23, lines 34, to page 24, line 4, which describes antisense compounds that do not cleave the target nucleic acid. This section states that a "region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide inhibition of gene expression."

Support for amendment to claim 2 and new claim 28, is found, for example, at page 26, lines 3-12, which describes pharmaceutically acceptable salts, including sodium salts (see also page 27, lines 29-33) of the compounds of the invention.

II. Patentability Arguments

As discussed during the personal interview of May 18, 2005, the amendments herein obviate the rejections under 35 USC §112, first paragraph.

Applicants submit that amendment of the claims to recite “non-cleaving” obviate the Examiner’s rejection of claims 1-2, 4-14, and 20-23 under 35 USC §103(a) in view of Chan (WO01/12789), further in view of Branch, Monia et al., and Agrawal et al. Chan discloses use of a RNA cleaving ribozyme to modulate expression of apolipoprotein B. Branch, Monia and Agrawal assertedly disclose optimization methods for use of antisense technology.

One of ordinary skill would not look to Chan because Chan addresses ribozyme compounds that cleave RNA in contrast to the claimed compounds which do not. Ribozymes function by a completely different mechanism from the non-cleaving compounds of the present invention. The non-cleaving compounds as claimed do not directly cleave target nucleic acids, but instead recruit and/or form the basis for complexes of the target with proteinaceous RNA-cleaving enzymes. Thus, even if a ribozyme inhibited expression of a nucleic acid, one of ordinary skill in the art would not find it obvious that a non-cleaving compound targeted to the same region would successfully inhibit expression of the target nucleic acid.

Further, one of ordinary skill in the art reading Chan, in view of Branch, Monia or Agrawal would have no reasonable expectation of success at generating the non-cleaving compound having certain functional properties as claimed herein. Chan discloses only a ribozyme that binds a single site in the apolipoprotein B gene. Agrawal and Branch focus on the problems associated with successfully generating an effective antisense compound, stating that “use of PS-oligonucleotides as antisense agents might not be as simple as initially expected,” (Agrawal, page 72, 2nd col.) and that “they [antisense] are far more difficult to produce than was originally anticipated,” (Branch, abstract). Simply because Agrawal, Branch or Monia assertedly disclose methods for generating or optimizing an antisense compound, it does not follow that one of ordinary skill in the art has a reasonable expectation of success at generating the antisense compound disclosed herein. In contrast,

Applicants disclose antisense compounds specific for apolipoprotein B that provide effective gene inhibition.

Thus, because the cited reference Chan is not relevant to the present claims, and because the references, even if taken in combination, do not provide a reasonable expectation of success of generating the claimed non-cleaving compounds, the rejection under 35 USC. §103 should be withdrawn.

As discussed during a telephonic interview of April 7, 2005, Applicants also provide herewith a copy of Declaration Under 37 CFR §1.132 of inventor Dr. Rosanne Crooke (Exhibit 1), which was also submitted in related application no. 10/147,096. This declaration provides data confirming that compounds that target the apolipoprotein B gene at a variety of sites throughout the molecule are effective at inhibiting apolipoprotein B expression and provides measurable beneficial effects on lipid profile and glucose levels in healthy animals and animal models of disease.

III. Conclusion

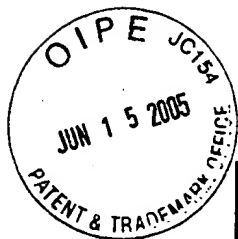
In view of the amendments and remarks made herein, Applicants submit that the application is now in condition for allowance and respectfully request expedited notification of the same.

Dated: June 16, 2005

Respectfully submitted,

By 
Katherine L. Neville

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Agent for Applicants



I hereby certify that this correspondence is being deposited with the U.S. Postal Service with sufficient postage as First Class Mail, in an envelope addressed to: Commissioner for Patents, P.O. Box 1450, Alexandria, Virginia 22313-1450, on the date shown below.

Dated: _____ Signature: _____

Docket No.: 30566/30039
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Rosanne M. Crooke et al

Application No.: 10/147,196

Group Art Unit: 1635

Filed: May 15, 2002

Examiner: Jon B. Ashen

For: ANTISENSE MODULATION OF
APOLIPOPROTEIN B EXPRESSION

DECLARATION UNDER 37 C.F.R. §1.132 OF DR. ROSANNE M. CROOKE

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Dear Sir:

I, Rosanne M. Crooke, declare that:

1. I am Director of the Cardiovascular Group at ISIS Pharmaceuticals, Inc., Carlsbad Research Center, 2292 Faraday Avenue, Carlsbad, California 92008. I received a Bachelors of Arts degree in Biology from Williams College in 1978 and a Doctor of Philosophy degree in Pharmacology from University of Pennsylvania in 1986. I have been employed at ISIS Pharmaceuticals, Inc. since 1989. I have been Director of the Cardiovascular Group since 2003.

2. I am a joint inventor of the subject matter described and claimed in the United States Patent Application Serial No. 10/147,196, entitled "Antisense Modulation of Apolipoprotein B Expression."

3. I am personally aware of results demonstrating that in healthy animals and in animal models of disease administration of a variety of compounds targeted to disparate regions of a mammalian ApoB genes aligning with base regions 3249-3268, 8886-8905, 8876-8895, and

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10159-10178 of SEQ ID NO: 3 not only inhibited the expression of a nucleic acid molecule encoding apolipoprotein B, but also provided beneficial effects of decreasing lipid levels.

4. I previously submitted a declaration, filed May 24, 2004, in the present application describing that administration of antisense compound 301012, targeting bases 3249-3268 of the human apolipoprotein B nucleotide sequence (SEQ ID NO: 3), to healthy primates inhibited apoB expression and decreased lipid levels in these animals, including total cholesterol, HDL- and LDL-cholesterol, and triglycerides. These data confirmed the beneficial effect of antisense inhibition of apolipoprotein B *in vivo* in primates not suffering from any disease.

5. Experiments with compounds targeting alternate sites of mammalian apolipoprotein B nucleotide sequences have shown that these alternate compounds are also effective at inhibiting apolipoprotein B expression and decreasing lipid levels. The targeted sites in mammalian apoB genes align with sites in the human apolipoprotein B gene (SEQ ID NO: 3) as illustrated in Exhibit A.

6. Antisense compound 147764 disclosed in the present application targets a site in the mouse apoB gene that aligns with bases 8886-8905 of the human apolipoprotein nucleotide sequence (SEQ ID NO: 3) (see Exhibit A). Administration of antisense compound 147764 to mice fed a high-fat diet, which are susceptible to hyperlipidemia-induced atherosclerotic plaque formation, led to decreased serum apolipoprotein B levels in treated animals, and also decreased serum total cholesterol and serum LDL-cholesterol. These results show a beneficial effect of the antisense compounds in mammals susceptible or at risk of cardiovascular disease.

7. Antisense compound 147483 disclosed in the present application targets a site in the mouse apoB gene that aligns with bases 8876-8895 of the human apolipoprotein nucleotide sequence (SEQ ID NO: 3) (see Exhibit A). Antisense compounds 147483 or 147764 were administered to *ob/ob* mice, a genetic model for type II diabetes and obesity characterized by hyperlipidemia and increased triglyceride levels, both of which are associated with an increase in cardiovascular disease. ApoB and lipid levels were measured. Antisense treated *ob/ob* mice showed decreased liver apolipoprotein B mRNA, reduced serum triglycerides and reduced serum total cholesterol. These results show a beneficial effect of antisense compounds in treating

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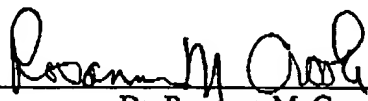
mammals susceptible or at risk for obesity, diabetes, cardiovascular disease, or other diseases associated with apolipoprotein B expression.

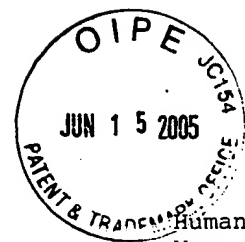
8. Antisense compound 233183 targets a site in the rabbit apoB gene that aligns with bases 1817-1836 of mouse apoB (SEQ ID NO: 10) and bases 10159-10178 of the human apolipoprotein B nucleotide sequence (SEQ ID NO: 3) (see Exhibit A). Administration of antisense compound 233183 to rabbits fed a normal diet decreased liver apoB mRNA levels in treated animals and reduced serum total cholesterol levels. These data confirm the beneficial effect of antisense inhibition of apolipoprotein B *in vivo* in mammals not suffering from any disease.

9. The results described above demonstrate that antisense compounds targeting a wide array of nucleotide sites (e.g. N-terminal, C-terminal, or internal nucleotide sequences) within the mammalian apolipoprotein B sequences effectively inhibit apolipoprotein expression levels in treated animals. In addition to decreasing apoB expression, the compounds also decrease lipid levels, resulting in, e.g., decreased cholesterol levels, decreased triglyceride levels and decreased LDL-cholesterol. These results confirm the statements made in the application regarding activity of the antisense compounds recited in the claims.

10. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful, false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code, and that such willful, false statements may jeopardize the validity of the application or any patent issued thereon.

Date 5/13/05


Dr. Rosanne M. Crooke



Mammalian Apolipoprotein B Sequences

Human GENBANK NM_000384.1; SEQ ID NO: 3 of ISPH-0664

Mouse GENBANK M35186.1; SEQ ID NO: 10 of ISPH-0664

Rabbit sequenced at Isis; SEQ ID NO: 810 of DOC-0216US

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Rabbit	-----	
Mouse	-----	
Human	CCCAGCCAGCCAGGGCCGCGAGGCCGAGGCCGAGCCGAGCCAGGAGCCGCCACCGC	120
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Mouse	-----	
Human	AGCTGGCGATGGACCCGCCGAGGCCGCGCTGCTGGCGCTGCTGGCGCTGCCTGCGCTGC	180
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Rabbit	-----	
Mouse	-----	
Human	CCAAGGAGAACTGACTGCTCTCACAAAAAGTATAGAATTACAGAAAATGATATACAAA	6600
Rabbit	-----	
Mouse	-----	
Human	TTGCATTAGATGATGCCAAATCAACTTTAATGAAAACTATCTCAACTGCAGACATATA	6660
Rabbit	-----	
Mouse	-----	
Human	TGATACAATTTGATCAGTATATTAAAGATAGTTATGATTTACATGATTTGAAAATAGCTA	6720
Rabbit	-----	
Mouse	-----	
Human	TTGCTAATATTATTGATGAAATCATTGAAAAATTAAAAAGTCTTGATGAGCACTATCATA	6780
Rabbit	-----	
Mouse	-----	
Human	TCCGTGTAAATTTAGTAAAAACAATCCATGATCTACATTTGTTTATTGAAAATATTGATT	6840
Rabbit	-----	
Mouse	-----	
Human	TTAACAAAAGTGGAAGTAGTACTGCATCCTGGATTCAAATGTGGATACTAAGTACCAA	6900
Rabbit	-----	
Mouse	-----	
Human	TCAGAATCCAGATACAAGAAAACTGCAGCAGCTTAAGAGACACATACAGAATATAGACA	6960
Rabbit	-----	

Mouse	-----	
Human	TCCAGCACCTAGCTGGAAAGTTAAAACAACACATTGAGGCTATTGATGTTAGAGTGCTTT	7020
Rabbit	-----	
Mouse	-----	
Human	TAGATCAATTGGGAACTACAATTCATTTGAAAGAATAAATGATGTTCTTGAGCATGTCA	7080
Rabbit	-----	
Mouse	-----	
Human	AACACTTTGTTATAAATCTTATTGGGGATTTTGAAGTAGCTGAGAAAATCAATGCCTTCA	7140
Rabbit	-----	
Mouse	-----	
Human	GAGCCAAAGTCCATGAGTTAATCGAGAGGTATGAAGTAGACCAACAAATCCAGGTTTTAA	7200
Rabbit	-----	
Mouse	-----	
Human	TGGATAAATTAGTAGAGTTGACCCACCAATACAAGTTGAAGGAGACTATTCAGAAGCTAA	7260
Rabbit	-----	
Mouse	-----	
Human	GCAATGTCCTACAACAAGTTAAGATAAAAGATTACTTTGAGAAATTGGTTGGATTATTG	7320
Rabbit	-----	
Mouse	-----	
Human	ATGATGCTGTGAAGAAGCTTAATGAATTATCTTTTAAACATTCATTGAAGATGTTAACA	7380
Rabbit	-----	
Mouse	-----	
Human	AATTCCTTGACATGTTGATAAAGAAATTAAAGTCATTTGATTACCACCAGTTTGTAGATG	7440
Rabbit	-----	
Mouse	-----	
Human	AAACCAATGACAAAATCCGTGAGGTGACTCAGAGACTCAATGGTGAAATTCAGGCTCTGG	7500
Rabbit	-----	
Mouse	-----	
Human	AACTACCACAAAAAGCTGAAGCATTAAACTGTTTTTAGAGGAAACCAAGGCCACAGTTG	7560
Rabbit	-----	
Mouse	-----	
Human	CAGTGTATCTGGAAAGCCTACAGGACACCAAAATAACCTTAATCATCAATTGGTTACAGG	7620
Rabbit	-----	
Mouse	-----	
Human	AGGCTTTAAGTTCAGCATCTTTGGCTCACATGAAGGCCAAATTCAGAGACTCTAGAAG	7680
Rabbit	-----	
Mouse	-----	
Human	ATACACGAGACCGAATGTATCAAATGGACATTTCAGCAGGAACCTTCAACGATACCTGTCTC	7740
Rabbit	-----	
Mouse	-----	
Human	TGGTAGGCCAGGTTTATAGCACACTTGTCACCTACATTTCTGATTGGTGGACTCTTGCTG	7800
Rabbit	-----	
Mouse	-----	
Human	CTAAGAACCTTACTGACTTTGCAGAGCAATATTCTATCCAAGATTGGGCTAAACGTATGA	7860
Rabbit	-----	
Mouse	-----	
Human	AAGCATTGGTAGAGCAAGGGTTCCTGTTTCTGAAATCAAGACCATCCTTGGGACCATGC	7920
Rabbit	-----	
Mouse	-----	
Human	CTGCCTTTGAAGTCAGTCTTCAGGCTCTTCAGAAAGCTACCTTCCAGACACCTGATTTTA	7980

Rabbit	-----	
Mouse	-----	
Human	TAGTCCCCCTAACAGATTTGAGGATTCCATCAGTTCAGATAAACTTCAAAGACTTAAAAA	8040
Rabbit	-----	
Mouse	-----	
Human	ATATAAAATCCCATCCAGGTTTCCACACCAGAATTTACCATCCTTAACACCTTCCACA	8100
Rabbit	-----	
Mouse	-----	
Human	TTCTTCTCTTACAATTGACTTTGTGCGAAATGAAAGTAAAGATCATCAGAACCATTGACC	8160
Rabbit	-----	
Mouse	-----	
Human	AGATGCAGAACAGTGAGCTGCAGTGGCCCGTTCCAGATATATATCTCAGGGATCTGAAGG	8220
Rabbit	-----	
Mouse	-----	
Human	TGGAGGACATTCTCTAGCGAGAATCACCTGCCAGACTTCCGTTTACCAGAAATCGCAA	8280
Rabbit	-----	
Mouse	-----	
Human	TTCCAGAATTCATAATCCCAACTCTCAACCTTAATGATTTTCAAGTTCTTGACCTTCACA	8340
Rabbit	-----	
Mouse	-----	
Human	TACCAGAATTCAGCTTCCCCACATCTCACACACAATTGAAGTACCTACTTTTGGCAAGC	8400
Rabbit	-----	
Mouse	-----GAATTCCAACCTCTCACCTCTCACATACAATTGAAATACCTGCTTTTGGCAAAC	55
Human	TATACAGTATTCTGAAAATCCAATCTCCTCTTTTACATTAGATGCAAATGCTGACATAG	8460
Rabbit	-----	
Mouse	TGCATAGCATCCTTAAGATCCAATCTCCTCTCTTTATATTAGATGCTAATGCCAACATAC	115
Human	GGAATGGAACCACCTCAGCAAACGAAGCAGGTATCGCAGCTTCCATCACTGCCAAAGGAG	8520
Rabbit	-----	
Mouse	AGAATGTAACAACCTCAGGGAACAAAGCAGAGATTGTGGCTTCTGTCACTGCTAAAGGAG	175
Human	AGTCCAAATTAGAAGTTCTCAATTTTGATTTTCAAGCAAATGCACAACCTCTCAAACCTA	8580
Rabbit	-----	
Mouse	AGTCCCAATTTGAAGCTCTCAATTTTGATTTTCAAGCACAAGCTCAATTCTGGAGTTAA	235
Human	AGATTAATCCGCTGGCTCTGAAGGAGTCAGTGAAGTTCTCCAGCAAGTACCTGAGAACGG	8640
Rabbit	-----	
Mouse	ATCCTCATCTCCAGTCTCTGAAGGAATCCATGAACTTCTCCAGTAAGCATGTGAGAATGG	295
Human	AGCATGGGAGTGAAATGCTGTTTTTGGAAATGCTATTGAGGGGAAATCAAACACAGTGG	8700
Rabbit	-----	
Mouse	AGCATGAGGGTGAGATAGTATTTGATGGAAAGGCCATTGAGGGGAAATCAGACACAGTCG	355
Human	CAAGTTTACACACAGAAAAAATACACTGGAGCTTAGTAATGGAGTGATTGTCAAGATAA	8760
Rabbit	-----	
Mouse	CAAGTTTACACACAGAGAAAAATGAAGTAGAGTTTAATAATGGTATGACTGTCAAAGTAA	415
Human	ACAATCAGCTTACCCTGGATAGCAACACTAAATACTTCCACAAATTGAACATCCCCAAAC	8820
Rabbit	-----	
Mouse	ACAATCAGCTCACCCCTTGACAGTCACACAAAGTACTTCCACAAGTTGAGTGTTCTTAGGC	475
Human	TGGACTTCTCTAGTCAGGCTGACCTGCGCAACGAGATCAAGACACTGTTGAAAGCTGGCC	8880
Rabbit	-----	
Mouse	TGGACTTCTCCAGTAAGGCTTCTCTTAATAATGAAATCAAGACACTATTAGAAGCTGGAC	535
		ISIS 147483
Human	ACATAGCATGGACTTCTTCTGGAAAAGGGTCATGGAAATGGGCCTGCCCCAGATTCTCAG	8940
Rabbit	-----	
Mouse	ATGTGSCATTGACATCTTCAGGACAGGGTCATGGAACTGGGCCTGTCCCAACTTCTCGG	595

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Human	ATGAGGGAACACATGAATCACAAATTAGTTTCACCATAGAAGGACCCCTCACTTCCTTTG	9000
Rabbit	-----	
Mouse	ATGAAGGCATACATTCTGCCAAATTAGCTTTACTGTGGATGGTCCCATTGCTTTTGTTG	655
Human	GACTGTCCAATAAGATCAATAGCAAACACCTAAGAGTAAACCAAACTTGGTTTATGAAT	9060
Rabbit	-----	
Mouse	GACTATCCAATAACATAAATGGCAAACACTTACGGGTCATCCAAAACTGACTTATGAAT	715
Human	CTGGCTCCCTCAACTTTTCTAAACTTGAAATTCAATCACAAGTCGATTCCCAGCATGTGG	9120
Rabbit	-----	
Mouse	CTGGCTTCCTCAACTATTCTAAGTTTGAAGTTGAGTCAAAGTTGAATCTCAGCACGTGG	775
Human	GCCACAGTGTCTAACTGCTAAAGGCATGGCACTGTTTGGAGAAGGGAAGGCAGAGTTTA	9180
Rabbit	-----	
Mouse	GCTCCAGCATTCTAACAGCCAATGGTCGGGCACTGCTCAAGGACGCAAAGGCAGAAATGA	835
Human	CTGGGAGGCATGATGCTCATTTAAATGAAAAGGTTATTGGAACCTTTGAAAAATTCTCTTT	9240
Rabbit	-----	
Mouse	CTGGTGAGCACAATGCCAACTTAAATGAAAAGTTATTGGAACCTTTGAAAAATTCTCTCT	895
Human	TCTTTTCAGCCCAGCCATTTGAGATCACGGCATCCACAAACAATGAAGGGAATTTGAAAG	9300
Rabbit	-----	
Mouse	TCTTTTCAGCACAACCATTGAGATTACTGCATCCACAAATAATGAAGGAAATTTGAAAG	955
Human	TTCGTTTTCCATTAAGGTAAACAGGGAAGATAGACTTCCTGAATAACTATGCACTGTTTC	9360
Rabbit	-----	
Mouse	TGGGTTTTCCACTAAAGCTGACTGGGAAAATAGACTTCCTGAATAACTATGCATTGTTTC	1015
Human	TGAGTCCCAGTGCCCAAGCAAGTTGGCAAGTAAGTGCTAGGTTCAATCAGTATAAGT	9420
Rabbit	-----	
Mouse	TGAGTCCCCGTGCCCAACAAGCAAGCTGGCAAGCGAGTACCAGATTCAATCAGTACAAAT	1075
Human	ACAACCAAAATTTCTCTGCTGGAAACAACGAGAACATTATGGAGGCCCATGTAGGAATAA	9480
Rabbit	-----	
Mouse	ACAATCAAACTTTTCTGCTATAAACAATGAACACAACATAGAAGCCAGTATAGGAATGA	1135
Human	ATGGAGAAGCAAATCTGGATTTCTTAAACATTCCCTTAAACAATTCCTGAAATGCGTCTAC	9540
Rabbit	-----	
Mouse	ATGGAGATGCCAACCTGGATTTCTTAAACATACCTTAAACAATTCCTGAAATTAAGTTGC	1195
Human	CTTACACAATAATCACAACCTCCTCCACTGAAAGATTCTCTCTATGGGAAAAACAGGCT	9600
Rabbit	-----	
Mouse	CTTACACGGAGTTCAAACCTCCCTTACTGAAGGATTCTCCATATGGGAAGAAACAGGCT	1255
Human	TGAAGGAATTCTTGAAAACGACAAAGCAATCATTGATTTAAGTGTAAGGCTCAGTATA	9660
Rabbit	-----	
Mouse	TGAAAGAATTTTGAAGACAACAAGCAATCATTGATTGAGTGTAAGGCTCAATATA	1315
Human	AGAAAAACAAACACAGGCATTCCATCACAATCCTTTGGCTGTGCTTTGTGAGTTTATCA	9720
Rabbit	-----	
Mouse	AAAAGAACAGTGACAAGCATTCCATTGTTGTCCCTCTGGGTATGTTTTATGAATTTATTC	1375
Human	GTCAGAGCATCAAATCCTTTGACAGGCATTTTGAAAAAACAGAAACAATGCATTAGATT	9780
Rabbit	-----	
Mouse	-----CAGAACATCGGAGACAACGCATTGGATT 28	
	TCAACAATGTCAATTCGTGGGACAGAAAATTTGAGAAAGTCAGAAACAATGCTTTACATT	1435
	* * * * *	
Human	TTGTCACCAAATCCTATAATGAAACAAAAATTAAGTTTGATAAGTACAAAGCTGAAAAAT	9840
Rabbit	-----	
Mouse	TTCTCACTAAATCTTANAATGAAGCAAAAATTAAGTTTGATAAGTACAAAGTTGAAAAAT 88	
	TTCTTACCACCTCCTATAATGAAGCAAAAATTAAGGTTGATAAGTACAAAACCTGAAAAAT	1495
	** * * * *	
Human	CTCACGACGAGCTCCCCAGGACCTTTCAAATTCCTGGATACACTGTTCCAGTTGTCAATG	9900
Rabbit	-----	
	CGCTCAACAGGCTCCCCAGGACCTTTCAGNCTCCTGGATACATTATTCCAATTTTCAATN	148

Mouse	CCCTTAATCAGCCCTCTGGGACCTTTCAAATCATGGCTACACTATCCCAGTTGTCAACA	1555
	* * * * *	
Human	TTGAAGTGTCTCCATTCAACATAGA-GATGTCGGCATTCCGGCTATGTGTTCCCAAAAGCA	9959
Rabbit	TTGAAGTATCTCCACTCACAATAGNAGACGTNAGCATTCAAGTCATGTGATCCCAAAATCA	208
Mouse	TTGAAGTATCTCCATTTGCTGTAGA-GACACTGGCTTCCAGGCATGTGATCCCCACAGCA	1614
	* * * * *	
Human	GTCAGCATGCCTAGTTTCTCCATCCTAGGTTCTGACGTCCGTGTGCCTTCATACACATTA	10019
Rabbit	ATAAGCACCCCCAATGTCACCATCCTGGATTCAAGCTTCTATGTGCCTTCATATACATTG	268
Mouse	ATAAGCACCCCAAGTGTACAATCCCTGGTCCTAACATCATGGTGCCTTCATACAAGTTA	1674
	* * * * *	
Human	ATCCTGCCATCATTAGAGCTGCCAGTCCTTCATGTCCCTAGAAATCT---CAAGCTTTCT	10076
Rabbit	GCTCTGCCATCCCTAGAGCTGCCAGTCTTCCATGTCCCCAGGAATCTACTCAAGGTCTCT	328
Mouse	GTGCTGCCACCCCTGGAGTTGCCAGTTTCCATGGTCCTGGGAATCTATTCAAGTTTTTC	1734
	* * * * *	
Human	CTTCCACATTTCAAGGAATTGTGTACCATAAGCCATATTTTTATTCTGCCATGGGCAAT	10136
Rabbit	CTCCAGATTTCAAGGAATTGAAAACCATTAACAATATTTTTATTCCAGCCATGGGCAAC	388
Mouse	CTCCAGATTTCAAGGGATTCAACACTATTGACAATATTTATATTCCAGCCATGGGCAAC	1794
	* * * * *	

Human	ATTACCTATGATTTCTCCTTTAAATCAAGTGTCACTCACTGAATACCAATGCTGAACTT	10196
Rabbit	ATTACCTATGAATTTTCCTTCAATCAACGATCATTACACTGAATACCAATGCTGGACTT	448
Mouse	TTACCTATGACTTTTCTTTTAAATCAAGTGTCACTCACTGAATACCAATGCTGGACTT	1854

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Human	TTTAACCAGTCAGATATTGTTGCTCATCTCCTTTCTTCATCTTCATCTGTCATTGATGCA	10256
Rabbit	TATAACCAATCAGACATTGTTGCCCATATCCTTTCTCCTCTTCATCTGTCATTGATGCA	508
Mouse	TATAACCAATCAGATATCGTTGCCCATTCCTTTCTCCTCTTCATTTGTCACCTGACGCC	1914

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Human	CTGCAGTACAAATTAGAGGGGCAC- CACAAGATTGACAAGAAAAGGGGATTGAAGTTAGC	10315
Rabbit	CTACAGTACAAATTAGAGGGGCACGCTCAAGTTTGA-----	543
Mouse	CTGCAGTACAAATTAGAGGGGAAC- ATCAGCTCTGATGCGAAAAAGGGGATTGAACTAGC	1973

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Human	CACAGCTCTGTCTCTGAGCAACAAATTTGTGGAGGGTAGTCATAACAGTACTGTGAGCTT	10375
Rabbit	-----	
Mouse	CACAGCTGTCTCTCTAACTAACAAATTTGTAAAGGGCAGTCATGACAGCACCATTAGTTT	2033

Human	AACCACGAAAAATATGGAAGTGTGAGTGGCAAAAACCACAAAAGCCGAAATTCCAATTTT	10435
Rabbit	-----	
Mouse	AACCAAGAAAAACATGGAAGCATCAGTGAGAACAACTGCCAACCTCCATGCTCCCATATT	2093

Human	GAGAATGAATTTCAAGCAAGAACTTAATGGAAATACCAAGTCAAAACCTACTGTCTCTTC	10495
Rabbit	-----	
Mouse	CTCAATGAACCTTCAAGCAGAACTTAATGGAAATACCAAGTCAAAACCCACTGTTTCATC	2153

Human	CTCCATGGAATTTAAGTATGATTTCAATTCTTCAATGCTGTACTCTACCGCTAAAGGAGC	10555
Rabbit	-----	
Mouse	ATCCATTGAACTAACTATGACTTCAATTCCTCAAAGCTGCACTCTACTGCAACAGGAGG	2213

Human	AGTTGACCACAAGCTTAGCTTGGAAAGCCTCACCTCTTACTTTTCCATTGAGTCATCTAC	10615
Rabbit	-----	
Mouse	CATTGATCACAAGTTCAGCTTAGAAAGTCTCACTTCCTACTTTTCCATTGAGTCATTAC	2273

Human	CAAAGGAGATGTCAAGGGTTTCGGTTCTTTCTCGGGAATATTAGGAAGTATTGCTAGTGA	10675
Rabbit	-----	
Mouse	CAAAGGAAATATCAAGAGTTCCTTCCTTTCTCAGGAATATTAGGAAGTGTGCCAATGA	2333

Human	GGCCAACACTTACTTGAATTCCAAGAGCACACGGTCTTCAGTGAAGCTGCAGGGCACTTC	10735
Rabbit	-----	
Mouse	AGCCAATGTATATCTGAATTC-----	2354

Human	CAAAATTGATGATATCTGGAACCTTGAAGTAAAAGAAAATTTGCTGGAGAAGCCACACT	10795
Rabbit	-----	
Mouse	-----	

Human	CCAACGCATATATTCCTCTGGGAGCACAGTACGAAAAACCACTTACAGCTAGAGGGCCT	10855
Rabbit	-----	
Mouse	-----	

Human	CTTTTTCACCAACGGAGAACATACAAGCAAAGCCACCCTGGAACCTCTCTCCATGGCAAAT	10915
Rabbit	-----	
Mouse	-----	

Human	GTCAGCTCTTGTTTCAGGTCCATGCAAGTCAGCCCAGTTCCTTCATGATTTCCCTGACCT	10975
Rabbit	-----	
Mouse	-----	

Human	TGGCCAGGAAGTGGCCCTGAATGCTAACACTAAGAACCAGAAGATCAGATGGAAAAATGA	11035
Rabbit	-----	
Mouse	-----	

Human	AGTCCGGATTCATTCTGGGTCTTTCAGAGCCAGGTCGAGCTTCCAATGACCAAGAAAA	11095
Rabbit	-----	
Mouse	-----	

Human	GGCACACCTTGACATTGCAGGATCCTTAGAAGGACACCTAAGGTTCCCTCAAAAATATCAT	11155
Rabbit	-----	
Mouse	-----	
Human	CCTACCAGTCTATGACAAGAGCTTATGGGATTTCTAAAGCTGGATGTAACCACCAGCAT	11215
Rabbit	-----	
Mouse	-----	
Human	TGGTAGGAGACAGCATCTTCGTGTTTCAACTGCCTTTGTGTACACCAAAAACCCCAATGG	11275
Rabbit	-----	
Mouse	-----	
Human	CTATTCATTCTCCATCCCTGTAAAAGTTTGGCTGATAAATTCATTACTCCTGGGCTGAA	11335
Rabbit	-----	
Mouse	-----	
Human	ACTAAATGATCTAAATTCAGTTCTTGTCATGCCTACGTTCCATGTCCCATTTACAGATCT	11395
Rabbit	-----	
Mouse	-----	
Human	TCAGGTTCCATCGTGCAAACCTTGACTTCAGAGAAATACAAATCTATAAGAAGCTGAGAAC	11455
Rabbit	-----	
Mouse	-----	
Human	TTCATCATTTGCCCTCAACCTACCAACACTCCCCGAGGTAAAATTCCTGAAGTTGATGT	11515
Rabbit	-----	
Mouse	-----	
Human	GTTAACAAAATATTCTCAACCAGAAGACTCCTTGATTCCCTTTTTTGAGATAACCGTGCC	11575
Rabbit	-----	
Mouse	-----	
Human	TGAATCTCAGTTAACTGTGTCCAGTTCACGCTTCCAAAAGTGTTTCAGATGGCATTGC	11635
Rabbit	-----	
Mouse	-----	
Human	TGCTTTGGATCTAAATGCAGTAGCCAACAAGATCGCAGACTTTGAGTTGCCACCATCAT	11695
Rabbit	-----	
Mouse	-----	
Human	CGTGCCTGAGCAGACCATTGAGATTCCCTCCATTAAGTTCTCTGTACCTGCTGGAATTGT	11755
Rabbit	-----	
Mouse	-----	
Human	CATTCCTTCCTTTCAAGCACTGACTGCACGCTTTGAGGTAGACTCTCCCGTGATAATGC	11815
Rabbit	-----	
Mouse	-----	
Human	CACTTGGAGTGCCAGTTTGAAAAACAAAGCAGATTATGTTGAAACAGTCCTGGATTCCAC	11875
Rabbit	-----	
Mouse	-----	
Human	ATGCAGCTCAACCGTACAGTTCTTAGAATATGAACTAAATGTTTGGGAACACACAAAAT	11935
Rabbit	-----	
Mouse	-----	
Human	CGAAGATGGTACGTTAGCCTCTAAGACTAAAGGAACACTTGACACACCGTGACTTCAGTGC	11995
Rabbit	-----	
Mouse	-----	
Human	AGAATATGAAGAAGATGGCAAATTTGAAGGACTTCAGGAATGGGAAGGAAAAGCGCACCT	12055
Rabbit	-----	
Mouse	-----	
Human	CAATATCAAAGCCCAGCGTTCACCGATCTCCATCTGCGCTACCAGAAAGACAAGAAAGG	12115
Rabbit	-----	

Mouse	-----	
Human	CATCTCCACCTCAGCAGCCTCCCCAGCCGTAGGCACCGTGGGCATGGATATGGATGAAGA	12175
Rabbit	-----	
Mouse	-----	
Human	TGACGACTTTTCTAAATGGAACCTTCTACTACAGCCCTCAGTCCTCTCCAGATAAAAACT	12235
Rabbit	-----	
Mouse	-----	
Human	CACCATATTCAAACTGAGTTGAGGGTCCGGGAATCTGATGAGGAACTCAGATCAAAGT	12295
Rabbit	-----	
Mouse	-----	
Human	TAATTGGGAAGAAGAGGCAGCTTCTGGCTTGCTAACCTCTCTGAAAGACAACGTGCCCAA	12355
Rabbit	-----	
Mouse	-----	
Human	GGCCACAGGGTCTTTTATGATTATGTCAACAAGTACCACTGGGAACACACAGGGCTCAC	12415
Rabbit	-----	
Mouse	-----	
Human	CCTGAGAGAAGTGTCTTCAAAGCTGAGAAGAAATCTGCAGAACAATGCTGAGTGGGTTTA	12475
Rabbit	-----	
Mouse	-----	
Human	TCAAGGGGCCATTAGGCAAATTGATGATATCGACGTGAGGTCCAGAAAGCAGCCAGTGG	12535
Rabbit	-----	
Mouse	-----	
Human	CACCACTGGGACCTACCAAGAGTGAAGGACAAGGCCCAGAATCTGTACCAGGAAGTGT	12595
Rabbit	-----	
Mouse	-----	
Human	GACTCAGGAAGGCCAAGCCAGTTTCCAGGGACTCAAGGATAACGTGTTTGATGGCTTGGT	12655
Rabbit	-----	
Mouse	-----	
Human	ACGAGTTACTCAAAAATTCATATGAAAGTCAAGCATCTGATTGACTCACTCATTGATTT	12715
Rabbit	-----	
Mouse	-----	
Human	TCTGAACTTCCCAGATTCCAGTTTCCGGGGAAACCTGGGATATACACTAGGGAGGAACT	12775
Rabbit	-----	
Mouse	-----	
Human	TTGCACTATGTTTCATAAGGGAGGTAGGGACGGTACTGTCCCAGGTATATTGAAAGTCCA	12835
Rabbit	-----	
Mouse	-----	
Human	TAATGGTTCAGAAATACTGTTTTCTATTTCGAAGACCTAGTGATTACACTTCCTTTTCA	12895
Rabbit	-----	
Mouse	-----	
Human	GTTAAGGAAACATAAACTAATAGATGTAATCTCGATGTATAGGGAAGTGTGAAAGATTT	12955
Rabbit	-----	
Mouse	-----	
Human	ATCAAAAGAAGCCCAAGAGGTATTTAAAGCCATTAGTCTCTCAAGACCACAGAGGTGCT	13015
Rabbit	-----	
Mouse	-----	
Human	ACGTAATCTTCAGGACCTTTTACAATTCATTTTCCAACATAAGATAACATTAAACA	13075
Rabbit	-----	
Mouse	-----	
Human	GCTGAAAGAGATGAAATTTACTTATCTTATTAATTATATCCAAGATGAGATCAACACAAT	13135

Rabbit	-----	
Mouse	-----	
Human	CTTCAATGATTATATCCCATATGTTTTTAAATTGTTGAAAGAAAACCTATGCCTTAATCT	13195
Rabbit	-----	
Mouse	-----	
Human	TCATAAGTTCAATGAATTTATTCAAAACGAGCTTCAGGAAGCTTCTCAAGAGTTACAGCA	13255
Rabbit	-----	
Mouse	-----	
Human	GATCCATCAATACATTATGGCCCTTCGTGAAGAATATTTTGATCCAAGTATAGTTGGCTG	13315
Rabbit	-----	
Mouse	-----	
Human	GACAGTGAAATATTATGAACTTGAAGAAAAGATAGTCAGTCTGATCAAGAACCTGTTAGT	13375
Rabbit	-----	
Mouse	-----	
Human	TGCTCTTAAGGACTTCCATTCTGAATATATTGTCAGTGCCTCTAACTTTACTTCCCAACT	13435
Rabbit	-----	
Mouse	-----	
Human	CTCAAGTCAAGTTGAGCAATTTCTGCACAGAAATATTCAGGAATATCTTAGCATCCTTAC	13495
Rabbit	-----	
Mouse	-----	
Human	CGATCCAGATGGAAAAGGGAAAGAGAAGATTGCAGAGCTTCTGCCACTGCTCAGGAAAT	13555
Rabbit	-----	
Mouse	-----	
Human	AATTAAAAGCCAGGCCATTGCGACGAAGAAAATAATTTCTGATTACCACCAGCAGTTTAG	13615
Rabbit	-----	
Mouse	-----	
Human	ATATAAACTGCAAGATTTTTCAGACCAACTCTCTGATTACTATGAAAAATTTATTGCTGA	13675
Rabbit	-----	
Mouse	-----	
Human	ATCCAAAAGATTGATTGACCTGTCCATTCAAACTACCCACACATTTCTGATATACATCAC	13735
Rabbit	-----	
Mouse	-----	
Human	GGAGTTACTGAAAAAGCTGCAATCAACCACAGTCATGAACCCCTACATGAAGCTTGCTCC	13795
Rabbit	-----	
Mouse	-----	
Human	AGGAGAACTTACTATCATCCTCTAATTTTTTAAAGAAATCTTCATTTATTCTTCTTTTC	13855
Rabbit	-----	
Mouse	-----	
Human	CAATTGAACTTTCACATAGCACAGAAAAAATTCAAAGTGCCTATATTGATAAAACCATAC	13915
Rabbit	-----	
Mouse	-----	
Human	AGTGAGCCAGCCTTGCAGTAGGCAGTAGACTATAAGCAGAAGCACATATGAACTGGACCT	13975
Rabbit	-----	
Mouse	-----	
Human	GCACCAAAGCTGGCACCAGGGCTCGGAAGGTCTCTGAACTCAGAAGGATGGCATTTTTTTG	14035
Rabbit	-----	
Mouse	-----	
Human	CAAGTTAAAGAAAATCAGGATCTGAGTTATTTTGCTAAACTTGGGGGAGGAGGAACAAAT	14095
Rabbit	-----	
Mouse	-----	

Human
Rabbit
Mouse

AAATGGAGTCTTTATTGTGTATCATA 14121

